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VIRULENCE FACTORS AND MECHANISMS OF *STREPTOCOCCUS AGALACTIAE* INFECTION IN TILAPIA (*OREOCHROMIS* SPP.): A REVIEW AND BIBLIOMETRIC ANALYSIS

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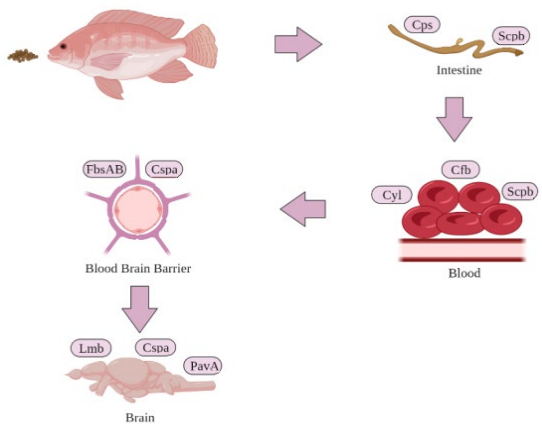
Graphical abstract



Abstract

Tilapia, a globally significant fish in aquaculture, faces the threat of *Streptococcus agalactiae* infections, leading to severe financial losses in the aquaculture sector. This emphasizes the need for a deeper understanding of virulence factors driving pathogenicity. This bibliometric review synthesizes scientific studies on the *S. agalactiae's* virulence factors, aiming to elucidate key genes influencing bacterial attachment and adhesion in fish hosts. Data from 115 relevant documents retrieved through Scopus database were analyzed using the VOSviewer application for keyword relationships. The results highlighted clusters related to virulence genes, infected organs, and clinical signs associated with *S. agalactiae* infections in tilapia. Capsular polysaccharides (CPs) emerged as a crucial virulence factor, with the brain being the major infected organ. Meningitis, lesions/necrosis, and hemorrhage were identified as primary clinical signs. The proposed mechanism outlines how *S. agalactiae* utilizes virulence genes to penetrate the fish's digestive system, evade the immune system, and cause systemic infections. In conclusion, this review emphasizes the importance of capsular polysaccharides as a key virulence factor in *S. agalactiae* infections in tilapia. Understanding the signaling response of Group B Streptococcus becomes crucial for devising effective vaccines to enhance the fish's immune responsiveness and detect *S. agalactiae* infections more efficiently.

Keywords: Bibliometric, *Streptococcus agalactiae*, virulence factor, capsular polysaccharide, VOSviewer

Abstrak

Tilapia, ikan yang mempunyai kepentingan global dalam akuakultur, menghadapi ancaman jangkitan *Streptococcus agalactiae*, yang menyebabkan kerugian kewangan yang besar dalam sektor akuakultur. Ini menekankan keperluan untuk pemahaman yang lebih mendalam mengenai faktor virulensi yang mendorong patogenisiti. Kajian bibliometrik ini mensintesis kajian saintifik mengenai faktor virulensi S. agalactiae, dengan tujuan untuk menjelaskan gen utama yang mempengaruhi keterikatan dan pelekatan bakteria dalam perumah ikan. Data daripada 115 dokumen yang berkaitan diperoleh melalui pangkalan data Scopus dan dianalisis menggunakan aplikasi VOSviewer untuk hubungan kata kunci. Keputusan menunjukkan kelompok yang berkaitan dengan gen virulensi, organ yang dijangkiti, dan tanda-tanda klinikal yang berkaitan dengan jangkitan S. agalactiae dalam tilapia. Polisakarida kapsul (CPs) dikenal pasti sebagai faktor virulensi yang penting, dengan otak menjadi organ utama yang dijangkiti. Meningitis, lesi/nekrosis, dan pendarahan dikenal pasti sebagai tanda-tanda klinikal utama. Mekanisme yang dicadangkan menerangkan bagaimana S. agalactiae menggunakan gen virulensi untuk menembusi sistem pencernaan ikan, mengelak sistem imun, dan menyebabkan jangkitan sistemik. Kesimpulannya, kajian ini menekankan kepentingan polisakarida kapsul sebagai faktor virulensi utama dalam jangkitan *S. agalactiae* pada tilapia. Memahami tindak balas isyarat Streptococcus Kumpulan B menjadi penting untuk merangka vaksin yang berkesan bagi meningkatkan tindak balas imun ikan dan mengesan jangkitan *S. agalactiae* dengan lebih cekap.

Kata kunci: Bibliometrik, *Streptococcus agalactiae*, faktor virulensi, polisakarida kapsul, VOSviewer

1.0 INTRODUCTION

Fisheries products are in high demand, particularly in Malaysia, and have a significant impact on national economic output. The fisheries field in Malaysia has provided employment opportunities and serves as an affordable protein source [1]. According to the Food and Agriculture Administration, Tilapia is one of the world's most important fish in aquacultures [2]. Worldwide production of tilapia fish increased by 4,850,000 metric tons in 2014. China, Indonesia, Egypt, Brazil, the Philippines, and Thailand are the main tilapia producers. Tilapia are omnivorous, highly adaptable, and are known for their rapid growth short life cycle [3-5]. Additionally, Tilapia possess resilient characteristics including regular spawning, early sexual maturity, and high survival of offspring that make this fish a choice of farmers worldwide [6].

The aquaculture industry is rapidly expanding, which has increased the risk of diseases such as *Streptococcus spp.* infections that lead to economic loss [7-8]. *S. agalactiae* is a group B streptococcus commonly found in warm climates. It infects different kinds of fish and is a major causative agent of mortality in tilapia farms, including those in Malaysia [9-10]. In the past decade, *Streptococcosis* has emerged as a main disease of the tilapia [11]. *Streptococcosis* infection caused by *S. agalactiae* was reported in Malaysia where a large number of deaths were recorded in floating cages with mortality rates reaching 50–70% within 3-7 days. Examinations using histopathological, biochemical and molecular tools were carried out from 2003 to 2012 on diseased tilapia where the infected fish with clinical signs such as septicemia were positive for *Streptococci* culture in their internal organs [12].

Streptococcus spp. is a prominent human and animal pathogen [13] with strong connections to several diseases and highly problematic diseases in freshwater fish farming that are constantly threatening the global tilapia sector [14]. The majority of outbreaks of Streptococcal infections in tilapia farms, resulting in significant mortality, tend to occur in the warmer months when the pathogenicity of *Streptococcus* spp. to tilapia is elevated [15]. Common species that cause infection in fish are *S. agalactiae*, *S. iniae* and *S. difficile*. *Streptococcus spp.* are well-known pathogens that causes an economic loss not only in aquaculture sectors but also infects chickens, camels, dogs, horses, monkeys, and humans [9]. The devastating impact of *S. agalactiae* on tilapia farms in Malaysia, as well as its global implications, necessitates a comprehensive understanding of the virulence factors driving its pathogenicity. This bibliometric review aims to synthesize existing scientific studies on *S. agalactiae's* virulence factors, offering insights into the key genes influencing bacterial attachment and adhesion within the host's body. By leveraging data from the Scopus application and employing the VOSviewer application for keyword

analysis, this study seeks to elucidate the intricate relationships among these virulence factors. The aim of this manuscript is to aid in the establishment of a model for *S. agalactiae* infection in tilapia, shedding light on crucial factors that facilitate its pathogenesis.

2.0 DATA COLLECTION AND ANALYSIS

Articles were searched using the keywords (Streptococcus AND agalactiae) AND (virulence OR pathogenicity) AND (tilapia OR Oreochromis))' using the Scopus database. A total of 126 documents were retrieved and then filtered by excluding certain document types such as reviews, notes and non-English documents. A total of 115 documents were included in the review. The Scopus file was then exported and analyzed in VOSviewer 1.6.19 using term analysis. The term analysis extracted and analyzed the keywords with a minimum three occurrences. The search field was the title and abstract of the selected documents [16]. All related keywords were further selected manually to categorize them under their corresponding virulence factors. The selected keywords were exported and arranged in Excel for the tabulation of the results. A bibliographic map was then created based on these selected keywords.

3.0 RESULTS

Bibliometric analysis of *S. agalactiae's* virulence factors revealed several groups of clusters which were virulence genes, infected organs and clinical signs. The overall network between all keywords is represented in Figure 1. Keywords related to capsular polysaccharides (CPs) had the highest occurrence among the virulence genes (Table 1). CPs are the main virulence factor that contributes to the evasion of the host's immune defense mechanisms which signified it as a crucial virulence factor of *S. agalactiae*. The brain was the major infected organ while the spleen, kidney and liver were often mentioned because these organs are involved in the immune response (Table 2). Regarding the clinical signs, there were three main signs observed in Tilapia infected with *S. agalactiae* (Table 3). Meningitis is the most mentioned sign as *S. agalactiae* affects the brain and causes damage to the brain tissue. Lesions and necrosis are indicative of tissue damage or necrotic areas, reflecting the destructive impact of the bacterial infection. Hemorrhage, marked by abnormal bleeding, underscores the vascular complications associated with *S. agalactiae*, contributing to the severity of the disease manifestation in these fish. Less frequently observed signs such as erratic swimming might also happen due to the brain damage causes erratic swimming behavior in infected fish. The connection of the respective related keywords (virulence genes, infected organs and clinical signs) was further illustrated in Figures 2, 3, and 4. Capsular polysaccharide, *CylE* and CAMP-factor were at the center of the connected keywords suggesting their importance as the virulence factors of *S. agalactiae*.

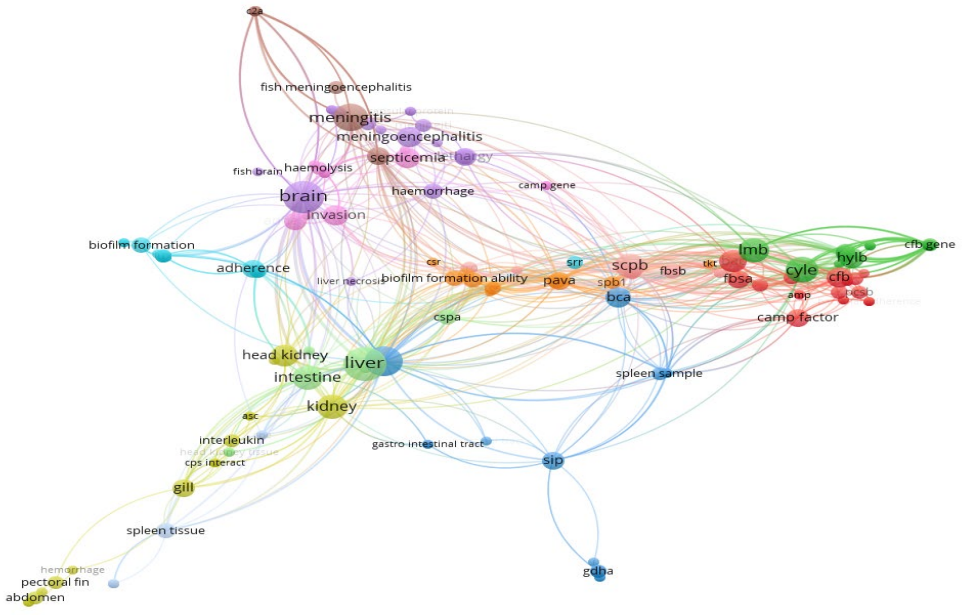


Figure 1 Relation between all keywords (Virulence genes, organs, clinical signs)

Table 1 Major virulence genes of *Streptococcus agalactiae*

Keywords	Related Keywords	Occurrence
Capsular polysaccharide	capsular antigen, capsular polysaccharide, capsular polysaccharide antigen, capsular protein, capsular regulation, capsular serotype, capsular serotyping, capsular type, capsular type ib, capsule, capsule polysaccharide, capsule thickness, cps, cps gene, cps gene cluster, cps h, cps interact, cps mutant, cps strain, cpsd, cpsg, polysaccharide capsule, sialylated capsular polysaccharide, sialylated cp	26
CylE	cyl, cyle, cyl gene coding, cytolytic toxin, cytotoxicity, haemolysin cytolysin, haemolysis, haemolysis strain, haemolytic activity, haemolytic toxin aera, hemolysin cytolysin, hemolysis activity, hemolytic activity, hemolytic bacterium, hemolytic cytolytic activity	24
CAMP-factor	camp factor, camp gene, cfb, cfb gene, cfb gene sequence	13
HylB	csr, csrr, hyaluronidase, hyaluronidase production, hyl, hyl b, hyl b, hylb, hylb virulence genes expression	13
Fibrinogen-binding protein	fbs, fbs a, fbs b, fbsa, fbsb, fibrinogen binding protein fbsa	11
Scpb	scpb, c2b, c3b, c4b, c5ap	11
BCA gene	alpha c protein, c protein alpha antigen, bp c alpha protein gene, bca, rib	10
Laminin-binding protein	lmb, lmb gene	9
Pili	biofilm formation, biofilm formation ability,pi 2b gene, pili backbone	9
Luxs	lux, luxs, luxs ai, luxs gene, quorum sensing inhibition	7

Table 2 Organ infected by *Streptococcus agalactiae*

Keywords	Related Keywords	Occurrence
Brain	bbb, blood brain barrier, brain, brain cell, brain tissue, brain tissues sample, fish brain, tilapia brain, tilapia brain cell, tilapia brain tissue	23
Spleen	spleen, spleen leukocyte, spleen sample, spleen tissue	17
Kidney	kidney, head kidney, head kidney tissue, tilapia kidney	15
Liver	Liver	14
Stomach	abdomen, intestinal epithelium, intestinal tract, intestine, gastro intestinal tract, intestinal sample	11
Gill	Gill	4
Pectoral fin	Pectoral fin	2
Heart	Heart	2
Eye	Eye	1
Operculum	Operculum	1

Table 3 Clinical signs of Tilapia infected with *Streptococcus agalactiae*

Keywords	Related Keywords	Occurrence
Meningitis	meningitis, meningoencephalitis, tilapia meningitis, brain damage, fish meningoencephalitis	18
Lesion/necrosis	lesion, melanosis, liver necrosis, necrosis, severe tissues necrosis, hepato necrosis, gastrointestinal damage, erosion	11
Haemorrhage	haemorrhage, hemorrhage, hemorrhage patch, septicaemia, septicemia	11
Exophthalmia	bilateral exophthalmia, exophthalmia, eye lesion	6
Lethargy	lethargy	4
Erratic swimming	Erratic swimming	3

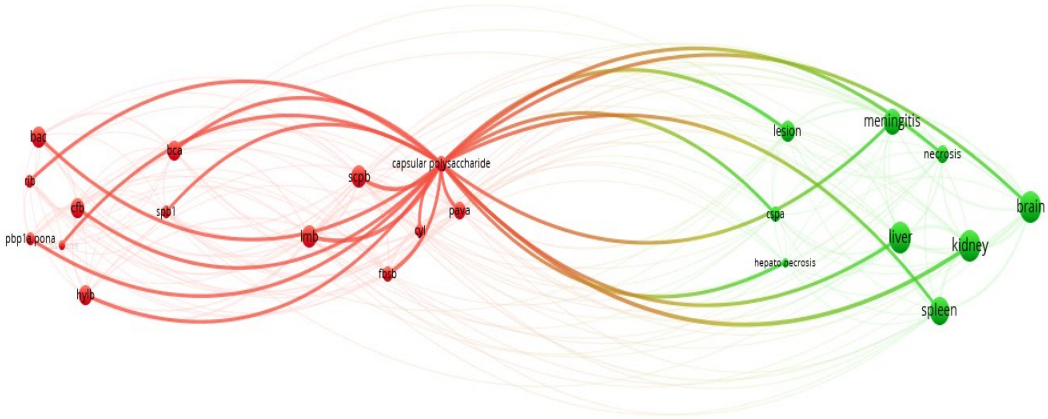


Figure 2 Relation between capsular polysaccharide with virulence gene, organs and signs

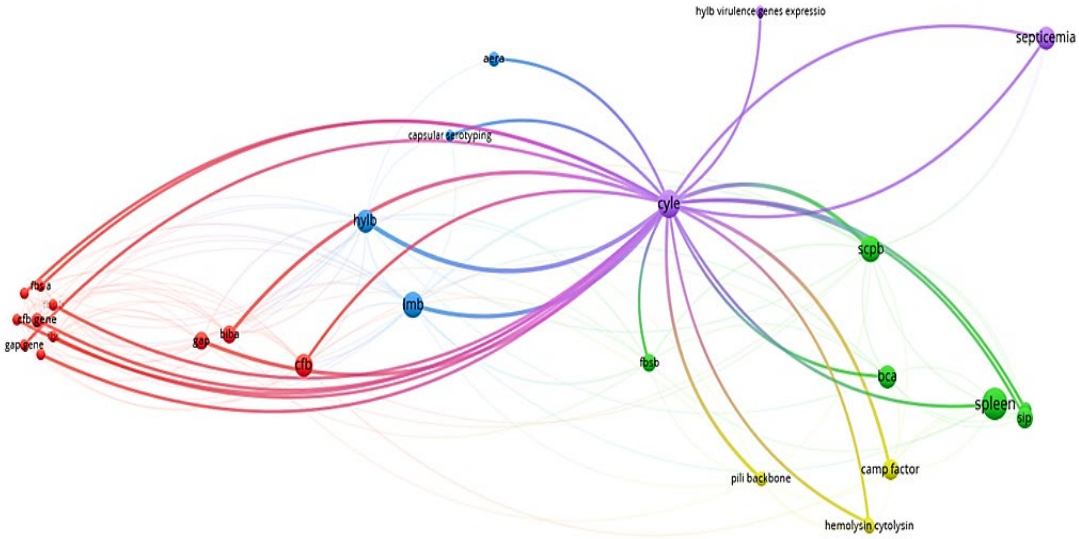


Figure 3 Relation between CylE with virulence genes, organs and clinical signs

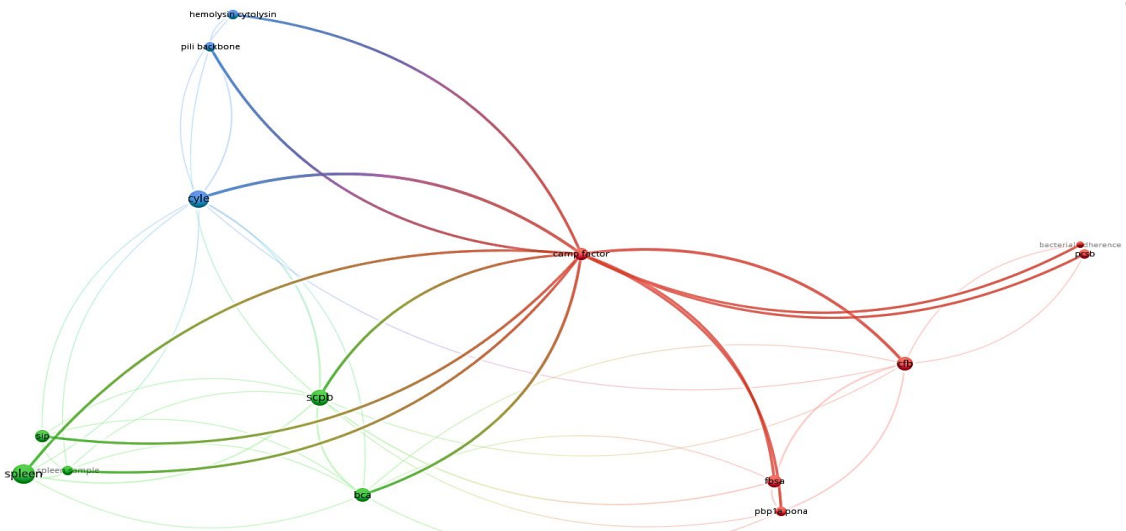


Figure 4 Relation between CAMP-factor with virulence genes and organs

4.0 DISCUSSION

4.1 Pathogenicity and Virulence Factor of *Streptococcus* spp.

The term "pathogenic" refers to the capability of a microorganism to induce disease or infect host cells [17]. Research indicates a total of 35 infectious species including *Streptococcus* spp., such as *S. pyogenes*, *S. mutans*, *S. agalactiae*, and *S. pneumoniae* [18]. *Streptococcus* spp. is implicated in fish diseases, with primary pathogens being *S. agalactiae* (GBS), *S. dysgalactiae*, and *S. iniae* [19]. GBS-infecting fish is categorized into different serotypes, with serotype Ia considered more pathogenic than serotype III [20]. Seafood resources like grouper, wild fish, and stingrays typically harbor serotypes Ia and Ib [21-22]. Genetic variation and plasmid presence play a role in determining the virulence and host specificity of various Streptococcal species, as plasmids carry genes related to drug resistance and virulence [23]. Moreover, several factors influence GBS virulence in fish, including temperature where an increase in temperature above 26°C may enhance the GBS virulence factors [24]. Additionally, a study reported that reducing the temperature from 35°C to 28°C decelerated *S. agalactiae* infection [25].

4.2 Capsular Polysaccharides (CPs)

Capsular polysaccharide (CP) is a common structure of GBS that evolved to protect itself from extreme environmental and host immune responses [26]. The GBS capsular, which consists mainly of polysaccharides, forms the outer layer of the bacterium [27] and resembles the sialylated polysaccharides present at the terminal ends of surface glycoproteins on immune cells [28].

Bacteria can evade the host's immune defenses and lead to systemic infection by mimicking the host molecularly in CPs bind to the host Siglecs. It then transmits a negative regulatory signal that destroys the host's inflammatory response homeostasis. The ability of CPs to block the formation of host complement factor (C3b) and prevent opsonization of phagocyte cells, establishing CPs as an important virulence factor for *S. agalactiae* [29]. Its importance as the major virulence factor is evidenced by the high occurrence number of keywords related to CPs as tabulated in Table 1. Recent research has continually showed CPs as key virulence factor in *S. agalactiae* not only in fish [30], but also causing infections in women, newborns [31-32], frog [33] as well as cows [34]. This highlights the importance of Cps in its ability to infect diverse organisms.

Galactose, glucose, N-acetylglucosamine and N-acetylneuraminic acid are among the components contained in CPs, including sialic acid (Sia) that protect from phagocytosis by affecting the active complement C3 deposited on the surface of bacteria. The sialic acid-dependent reduction of C3 deposition is associated with decreased formation of C5a, a crucial complement-derived chemoattractant [35]. In Nile tilapia, Cps plays a key role in *S. agalactiae's* ability to evade macrophage phagocytosis. Yang *et al*. reported that the terminal sialic acid residues in CPs is a crucial in the ability of *S. agalactiae* immune evasion and might act as immune escape site [36].

GBS can be classified into 10 capsular serotypes which are Ia, Ib and II–IX [37]. Ia, Ib, and III were discovered from fish infected with *Streptococcus spp.* [17], while in another study, it was found that only 2 serotypes which were Ia and III had been isolated from Tilapia farms in Thailand [38]. Capsules of GBS serotype Ib strains affect *S. agalactiae* adhesion in the tilapia intestinal epithelium [36].

4.3 *CylE*

The *CylE* gene is essential for hemolysin production in *S. agalactiae* [39] which is associated with the tissue damage process [40]. *CylE* is the structural gene which is also involved in the breakdown of red blood cells (β-hemolysis/cytolysis) [41]. β-Hemolysin/cytolysin, encoded by *CylE* gene, helps the bacteria to penetrate the epithelial and endothelial of host cell and to withstand phagocytosis. The surge in *cylE* expression at 35°C was consistent with the increasing hemolytic activity and viability of GBS [39]. Several studies indicated that β-hemolysin serves as a virulence factor impacting the viability of *S. agalactiae* [42-43] and facilitates infection in non-hemolytic strains, enabling them to evade the host immune response and remains inactive until reactivated by favorable conditions. The presence of *cylE* genes aids in promoting invasion to rapidly spread through the bloodstream and infected host organs [19].

4.4 CAMP-factor

Multiple strains of *S. agalactiae* have been identified in both humans and fish, with the presence of genes such as CAMP, Bsp and PcsB being detected [44]. Most GBS strains secrete extracellular proteins known as the CAMP (Christie–Atkins–Munch–Petersen) factor. The gene encoding CAMP factor in *S. agalactiae's* is *cfb* [45], which can bind to a glycosylphosphotidylinositol (GPI)-anchored protein to facilitate host cell lysis [46].

The pathogenesis of GBS in fish depends on the CAMP factor which act as a cytolytic and pore-forming toxin that contributes to the cell lysis process [46]. Additionally, recombinant CAMP factor from *S. agalactiae's* was shown to form pores in the host's cell membrane leading to cellular destruction [46]. CAMP-like factors are also produced by groups A, C, and G *Streptococcus,* but their coding gene sequences share relatively low homology. Hence, the *Cfb* gene can be used for molecular identification [47].

The CAMP reaction is commonly employed as a presumptive diagnosis for *S. agalactiae* [48] and the phenotypic characterization of *S. agalactiae*, the

hemolysis reaction caused by the CAMP factor can be used. In addition, elevated temperatures can upregulate *S. agalactiae* virulence factors such as CAMP, Bsp, and Pcbs. This in turn enhances adhesion, divisions and pore formation in the host cells [49]. PcsB and CAMP factors have emerged as promising candidates for next-generation vaccine against GBS, given their role in host tissue damage, as highlighted by Li and colleagues [50].

4.5 *HylB*

Hyaluronidase is one of the key virulence factors in *S. agalactiae* where deactivation of the *HylB* gene has been shown to impair the *S. agalactiae's* ability to cross the blood-brain barrier [51]. The *HylB* gene, encoding hyaluronate lysase, which facilitates the spread of GBS by degrading hyaluronic acid polymers. Inactivation of *HylB* gene leads to the absence of extracellular hyaluronidase which reduces survival of *S. agalactiae* in macrophages and increases inflammatory response [52]. A previous study also demonstrated that baicalin, a flavone glycoside, effectively inhibits hyaluronidase production by *S. agalactiae* [53].

4.6 Fibrinogen-binding Protein & Streptococcal C5a Peptidase (Scp)

The transcription of the *fbsA* and *fbsB* genes mediates the binding of GBS to host extracellular matrix fibrinogen and plays role in regulating GBS adhesion and invasion into host cells [53]. The adhesion gene cluster regulates bacterial adhesion to host cell surfaces and fibrinogen-binding proteins, enabling their attachment to epithelial cells [54-55]. FbsA, a highly repetitive cell wall-bound adhesin that enhances GBS adherence to human epithelial cells [56], while fbsB plays a crucial role in *S. agalactiae's* invasion into these cells [57]. However, the impact of fbsA deletion in Thai ST7 strains on pathogenicity in fish remains unclear.

Fibrinogen-binding proteins are essential for colonization due to their ability to bind extracellular matrix fibrinogen. The *pavA* gene, encoding the virulence A protein, acts as a fibronectin adhesin, facilitating bacterial colonization and binding to fibrinogen [58]. Adherence to host tissue represents a crucial initial step for bacterial entry and aids in avoiding host detection [59]. A prior study reported that the SrtA mutant strain of *S. agalactiae* exhibited a significant reduction in binding to fibrinogen and fibronectin compared to the wild-type strain [60].

The *scpB* gene encodes C5a peptidase, which binds to fibronectin and contribute to immune evasion [53]. C5a peptidase is a binary protein that breaks down C5a, mediates adhesion to host molecules and thereby aiding in evading the host immune system. [61]. By facilitating adhesion and immune evasion, Scpb significantly contributes to the overall virulence of *S. agalactiae*. The absence of *scpB* and *lmb* genes in some pathogenic strains suggests that peptidase C5a and laminin-binding protein activity may not essential for pathogenesis in all cases [62].

4.7 Other Virulence Genes

Virulence factors in *S. agalactiae* include components that facilitate adhesion and entry (e.g. Lmb, BibA, DltA, PavA, and pili), promotes colonization (e.g. Csp and Gap), enables immune evasion (e.g. CpsA, ScpB, and sialic acid), and induces cytotoxicity (e.g. Cfb, CylE and HylB). These factors are essential for facilitating entry of Group B Streptococcus (GBS) into host cells, as well as in ensuring its persistence and spread [25].

The surface-lipoprotein encoded by the *lmb* gene, as a laminin-binding protein, works in conjunction with the C5a peptidase (encoded by scpB) to enhance *S. agalactiae* adherence to host cells [53-63]. The *pavA* gene encodes the virulence A protein, a fibronectin adhesin that promotes bacterial colonization [58]. BibA, a conserved cell wall protein in the GBS adhesin gene cluster, binds to complement C4 protein, facilitating adhesion to epithelial cells. Studies have indicated that BibA is immunogenic in the host and imparts resistance to phagocytic killing, thereby contributing to bacterial survival [63]. Moreover, it is hypothesized that the coordinated actions of virulence gene components, including evasins, invasins, and adhesins may synergistically enhance GBS virulence in host cells [61].

4.8 Proposed mechanism

S. agalactiae can enter the fish digestive system via contaminated water or feed. Under the harsh conditions of the intestinal environment. *Cps* gene enhances the production of capsular polysaccharides that mimics host molecules involved in the fish immune response. This molecular mimicry decreases phagocytosis and enhances adherence to intestinal epithelial cells [26].

Additionally, the *ScpB* gene contributes to immune evasion by degrading C5a protein, a key component of the immune response [53]. Furthermore, *ScpB* can reduces neutrophil recruitment and binds with fibronectin to invade epithelial cells [601.

The *Cfb* gene, which encodes the CAMP-factor, enhances cell lysis (co-hemolysis), facilitates *S. agalactiae* translocation from the epithelial cells into bloodstream [46]. Hemolysin produced by CylE lysis red blood cells, leading to septicemia in the fish.

Fibrinogen-binding proteins (FbsA and FbsB) facilitate GBS adherence and invasion by binding to host extracellular matrix fibrinogen [61]. The serine protease (*CspA*) may modulate the immunological response by inactivating the CXC chemokine produced by the host.

Upon crossing the blood-brain barrier (BBB), the *pavA* gene produces a protein, encoding fibronectin-binding adhesin, facilitating colonization of *S. agalactiae* in the fish's brain [58]. The *Lmb* gene supports adhesion and invasion of brain tissue, while

cspA may further contribute to immune evasion in the host. The proposed pathway of *S. agalactiae* infection through the intestinal tract is illustrated in Figure 5.

S. agalactiae may also enter the fish's body through the gills. The bacterium may utilize its CPs to adapt to the challenging conditions within the gills. Additionally, it mimics host surface molecules as a strategy to evade detection by the immune system. The *Lmb* might also facilitates adherence and invasion of host tissues. However, comprehensive studies examining gill-mediated infection pathways of *S. agalactiae* remains limited.

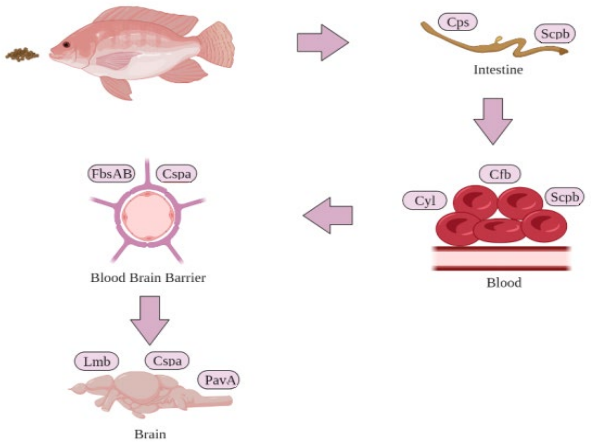


Figure 5 *Streptococcus agalactiae* infection pathway through the intestine

4.9 Future Research and Recommendations

Novel approaches are needed to effectively combat *S. agalactiae* and other Group B Streptococcus (GBS) pathogens. While conventional formalin-killed vaccines remain widely used, they are labor-intensive to produce; in contrast, newer synthetic vaccines have demonstrated promising potential. For instance, Bahadori *et al*. developed a synthetic carbohydrate-based vaccine using capsular polysaccharides (CPs), achieving high yield [64]. Similarly, Jessouroun *et al*. isolated and characterized CPs from the *S. agalactiae* Brazilian RS-72 strain, which demonstrated high purity and was recommended for conjugate and subunit vaccine development [65].

Given the central role of CPs in immune evasion, targeting this major virulence factor is essential. The CPs gene enables *S. agalactiae* to replicate inside the fish host and escape immune detection. Therefore, the development of a novel vaccine specifically targeting capsular polysaccharides is warranted. One potential approach is a polysaccharide-based vaccine devoid of live *S. agalactiae*, designed to enhance antigen recognition and neutralization by the host immune system. A thorough understanding of GBS signaling pathways involved in immune evasion is crucial for effective vaccine design.

In addition to CPs-targeted strategies, other advanced technologies are emerging in vaccine research. For example, CRISPR has shown potential in inhibiting key virulence genes. Nie *et al*. used CRISPR-RNA to target the *cpsA* gene of a highly virulent *S. agalactiae* strain and inhibited capsular polysaccharide production [66]. Furthermore, glycolipid biosynthesis pathways, such as those involving Lipid-a, could be additional novel targets for vaccine development [67].

5.0 CONCLUSION

In summary, capsular polysaccharides represent the primary virulence factor facilitating Streptococcus entry into the host. *Cps* and *ScpB* facilitate immune evasion and adherence, while *Cfb*, *CylE*, and *ScpB* enhances hemolysis. The brain is the main target organ of *Streptococcus* spp, facilitated by *PavA*, *CspA*, and *Lmb* genes, often resulting to meningitis and abnormal swimming behavior of infected fish. FbsAB and CspA assist in breaching the Blood-Brain Barrier. This multi-stage pathogenic highlights the need for targeted strategies in streptococcosis prevention and control.

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Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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